Dissociating the lesion sites that cause different types of speech production difficulties

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Abstract

Spoken language ability is one of the most complex functions the brain performs, and sets humans apart from other animals. Loss of language ability following brain injuries such as stroke is devastating. The aim of this study was to examine the extent to which lesion site detected by magnetic resonance imaging (MRI) can predict language performance following stroke. Voxel-based morphometry (VBM) analysis was used to find correlations between language performance and brain lesions. The gray matter images of 94 stroke patients and 64 healthy controls (all of whom were right handed) and their language test scores in eight single-word language CAT tests (Comprehensive Aphasia Test) were included in the analysis. Multiple regression was performed at every voxel of the brain to find those voxels where gray matter density was low and behavioural performance was poor

The results of our VBM analyses showed that acquired speech production deficits were most likely following lesions to any of the following brain regions: the left frontal orbitalis, left insula (anterior and posterior), left caudate nucleus, left thalamus, and right cerebellum. Lexical phonological retrieval was more impaired if the damage was restricted to the left ventral frontal areas, extending into the anterior insula, and the caudate nucleus, while sublexical phonological retrieval was more impaired if damage was restricted to the left posterior insula and left thalamus. This double dissociation between the anterior and the posterior insula has not been reported previously. The results also showed that phonological short-term memory is more dependent upon the left supramarginal gyrus, consistent with previous functional imaging studies of healthy subjects. Once these task-specific effects had been accounted for, there remained a large area of the posterior frontal cortex where damage impairs performance of all eight speech language tasks.

Contents

1.Introduction

Our unique ability to communicate through language is one of the most fascinating functions that the human brain performs. The ability to communicate complex ideas and thoughts through language has captured the interest of philosophers, psychologists, and neurologists alike throughout history. In the field of cognitive neuroscience, linguistic ability is one of the most extensively studied of all cognitive domains. This introduction will be divided broadly into two parts: the first will deal with the ways in which language is studied in the brain, while the second will give an overview of the current understanding of language and the brain, concentrating primarily on speech production.

1.1 Methods to study the brain

1.1.1 Neuropsychology

The way in which language is organised in the brain has been the subject of extensive investigation and is the primary question in the field of the neuroscience of language. Although the recent development of functional and structural imaging techniques has aided greatly studies of the linguistic brain, language studies have traditionally relied upon anatomical methods alone. In these classical patient studies, inferences were drawn between impaired cognitive functions and structural lesions, usually discovered post-mortem, to establish a structure-function relationship.

Paul Broca's discovery that a region in the left inferior frontal cortex is involved in speech production is a classic example of the traditional anatomical clinico-pathological approach. In 1861, Paul Broca described a patient named Le Borgne who had severe speech production deficits (Broca, 1861). Le Borgne soon became known as 'Tan' since the monosyllabic sound 'tan' was the only thing he was able to say. After Tan's death, Broca conducted an autopsy and

reported that Tan had a lesion on the surface of the left inferior frontal cortex. Not long after Tan's death, Broca described another patient, a Mr Lelong, who also had a severe speech production deficit and was only able to say five words (Dronkers et al., 2007). After Mr Lelong's death, it was found that he too had a lesion in the left inferior frontal cortex. Broca concluded that this region of the frontal cortex is the site responsible for speech production, particularly articulation, *'the faculty to coordinate the movements which belong to articulate language'*, which when damaged makes articulation impossible (Broca, 1861; Coltheart, 2001). Broca believed that these patients had intact language comprehension, in that they were able to understand what was said to them, but that the motor aspect of their speech was impaired.

Although Broca's proposal that speech production is localised in the left inferior frontal cortex received a mixed response initially, it was supported in 1874 by Carl Wernicke's complemetary publication describing a condition he termed *sensory aphasia.* Wernicke described several patients who had profound speech comprehension problems with fluent but meaningless speech following damage to the superior temporal regions of the dominant left hemisphere (Wernicke, 1874). Wernicke proposed that this area of the brain was responsible for language comprehension. Since then these two discrete areas became known as Broca's and Wernicke's areas respectively. Patients with deficits in language production are known as having Broca's aphasia, while those with speech comprehension deficits are known as having Wernicke's aphasia.

Although much pioneering work has been based on the anatomical clinico-pathological approach this method of studying the brain has several limitations;

i.) The definition of 'Broca's area' is confusing and controversial since the precise neuroanatomical location varies between individuals (Davis et al., 2008). Also, disorders such as 'Broca's aphasia' are rarely related to consistent lesion sites (Basso et al., 1985). Studies have also shown that many patients with non-fluent aphasias have lesions lying outside of 'Broca's area (Dronkers, 1996; Wise et al., 1999), while damage to Broca's area does not always result in Broca's aphasia, and has even been associated with impairments in domains other than language (Davis et al., 2008)

ii.) The classical aphasia model often classifies patients into syndromes, i.e. 'Broca's aphasia'. Although such syndrome-based classification is able to give a 'general idea' about what is impaired in a patient, it does not define any cognitive components that may be involved (Demonet et al., 2005).

iii.) Like other cognitive functions of the brain, language involves complex interactions between many neural networks, working together to carry out various cognitive processes that are involved in language. Impairments therefore may result from a disruption in this complex interaction between various brain regions, not in themselves directly affected by the lesion (Demonet et al., 2005)

1.1.2 Neuroimaging and Cognitive Tests

The development of functional and structural imaging techniques in the last half of the century, has greatly advanced our understanding of language in the brain. Although many questions still remained unanswered, neuroimaging techniques have allowed greater precision in defining the

geographic location of lesions, and more importantly they have allowed in-vivo assessment of the activity in the brain during various tests of cognitive processes. Using these cognitive tests together with neuroimaging techniques allows the identification of various brain regions that may contribute to subtle cognitive processes not possible with the anatomical methods alone. They also allow iterative testing based on the identified pathological process and thus a level of statistical confidence not possible with the single post-hoc assessment at autopsy.

An example of such a cognitive test is the Comprehensive Aphasia Test (CAT) (Swinburn K, 2004). CAT comprises tests of language performance at different processing levels; both sentence-level and single-word levels. These tests are designed to tap into subtle cognitive processes involved in language. The current understanding is that there are at least two separate systems involved in word reading. This idea of a dual reading system arose from the observation reported by Marshall and Newcombe in 1973 that some aphasic patients are able to read non-words (pseudowords, or made up nonsense words) and regular words (e.g. 'mint'), but made 'regularisation' errors for irregular words (meaningful words with irregular spelling such as 'pint', and 'yacht') (Marshall and Newcombe, 1973). Marshall and Newcombe also describe two other patients who were completely unable to read non-words, but were able to read regular and irregular (e.g pint) words equally well. This 'double dissociation' suggested there must be at least 2 ways in which the sounds of the words can be generated through reading. These routes are sometimes referred to as *lexical* and *sublexical*. Firstly, regular and non-words can be read via the sublexical system by following 'rules' and sounding out each letter (the process is also known as the orthography-to-phonology conversion, or grapheme-phoneme conversion). However, reading irregular words via the sublexical system would lead to regularisation errors (e.g. reading *pint* to rhyme with *mint*) since they do not follow the 'rules'. The second way in which words can be read is by activating the semantic-lexical phonology representation system, which contains representations of the 'whole' words. Non-

words are made up words which do not exist and are therefore unlikely to have a representation in the semantic-lexical system. Thus, regular words can be read via both the sublexical and the lexical systems, while non-words can only be read via the sublexical system and irregular words via the lexical system (Hillis, 2001).

1.1.3 Voxel-based analysis

Recently a new technique for lesion analysis has been developed. This is known as voxel – based morphometry (VBM) or voxel-based lesion-symptom mapping (VLSM, (Bates et al., 2003). Previously, before the invention of this method, lesion studies usually relied on one of two other methods; i.) The first method is to classify patients on the basis of their lesions and test for the difference in their behavioural performance against the controls, this is known as the *region of interest* (ROI) method, ii.) The second method is to classify patients on the basis of their behavioural deficits and do a lesion overlap to find the areas most commonly damaged in such deficits. This method is known as the *behaviour-defined* method (Dronkers et al., 2004). Although these methods have been very informative, important information is likely to be lost when patients are forced into one category or another. For example, by grouping patients on the basis of a particular region of interest, lesions in other areas that may contribute to behaviours may be lost (Bates et al., 2003).

VLSM in contrast, is not at risk of loosing important information since it does not require patients to be grouped on the basis of their behaviour or lesion sites (Bates et al., 2003; Kimberg et al., 2007). Instead, VLSM involves mapping the relationship between the lesion site and behavioural performance on a voxel-by-voxel basis across the whole brain (Bates et al., 2003; Kimberg et al., 2007). However, a limitation of VLSM is that it uses a categorical measure of brain damage (damaged or not damaged). In contrast, the method we used in this

project used voxel-based morphometry (VBM) that uses continuous measures of both behaviour and gray or white matter density.

1.2 Current Understanding of language

This section aims to give a general overview about current concepts on the neurology of language, concentrating primarily on speech production. The most common concept when thinking about language is that the language system is divided into language production and language comprehension with each supported by distinct and separate brain regions as proposed originally by Broca and Wernicke (Broca, 1861; Wernicke, 1874). However, recent evidence has shown that the brain regions underlying these broad functions are not confined to just Broca's and Wernicke's areas (Ackermann et al., 2007; Borovsky et al., 2007; Dronkers, 1996; Ogar et al., 2006; Ogar et al., 2007; Wise et al., 1999). For example, a recent study using VLSM to investigate the brain areas involved in language comprehension revealed that lesions in Broca's and Wernicke's areas did not significantly affect language comprehension. Instead, areas that were found to affect language comprehension when damaged included the posterior temporal gyrus, and the underlying white matter, the anterior superior temporal gyrus, the superior temporal sulcus and angular gyrus, and in the frontal cortex Brodmann's areas 46, and 47 (Dronkers et al., 2004)

1.2.1 Speech production

Our ability to produce fluent speech and convey complex ideas coherently is one of the most complex skills humans have. In order for us to produce fluent and meaningful speech, we must first activate the representation of the word that is going to be said, then the word must be retrieved (lexical retrieval), and the sounds of the words must be assembled, this must then be translated into appropriate articulatory plans before the actual speech is produced (Nickels, 2001; Price, 2004).

Although the exact regions (and their functions) that contribute to speech production remain unknown, studies have shown that the system for speech production is very left cerebral hemisphere-lateralised in right-handed individuals. To understand spontaneous speech production, some studies concentrate on the neural substrates of single retrieval and production (Indefrey and Levelt, 2004), while others have examined the brain involved in the motor aspects of speech (Ackermann et al., 2007; Ackermann and Riecker, 2004; Amici et al., 2007; Blank et al., 2002; Borovsky et al., 2007; Croot et al., 1998; De Smet et al., 2007; Dronkers, 1996; Hillis et al., 2004; Murdoch, 2001; Ogar et al., 2006; Ogar et al., 2007). Together these studies have revealed a number of areas that seem to play an important role in speech production including, the anterior insula, the superior temporal cortex, the basal ganglia, the fusiform gyrus, inferior frontal gyrus, and the cerebellum. The definitions of Broca's area and Broca's aphasia are not so informative, since damage to Broca's area does not always result in Broca's aphasia, and as mentioned previously patients with speech production deficits have been shown to have lesions lying outside of Broca's area (Amici et al., 2007; Basso et al., 1985; Borovsky et al., 2007; Dronkers, 1996; Ogar et al., 2006; Ogar et al., 2007).

1.3 This Study

This study aimed to investigate the extent to which lesion site can predict behavioural performance after stroke. As mentioned previously, patient-lesion studies often encounter problems such as: 1.) variability in lesion locations and behavioural performance across patients, 2.) a lesion in a particular location can be associated with different behavioural deficits, 3.) a particular behavioural deficit can be associated with different lesion sites. The solution to this problem is to do a patient correlative population study and to look at the probability that a particular lesion causes a particular deficit and vice versa. Thus, the current study aims to answer the question by performing multiple-regression at every voxel of the

brain across a population of patients, and find the voxels where gray matter density is low when performance is also low.

In this study, we aim to find the locations where lesions correlate with impaired language processes, including reading, lexical phonological retrieval, sublexical phonological assembly, and verbal-short term memory. Using the results obtained from multiple regression analyses, we then aim to examine the patients' behavioural test scores (CAT scores), to see if damage to those regions actually predict behavioural performance reflected in CAT scores.

2. Methods

2.1 Participants

The study was approved by the Joint Ethics Committee of the Institute of Neurology (Univerisity College London), and the National Hospital for Neurology and Neurosurgery. Informed consent was obtained from a total of 64 right-handed volunteers with no history of neurological or psychiatric disorders and 94 stroke patients who were right-handed before the stroke. The control group consisted of 25 males (age 21-74 years, mean 55.6 years), and 39 females (age 22-77 years; mean 59.4 years). The stroke patients group included 60 males and 34 females. English was the first language of all participants.

2.2 Behavioural assessment

Patients' language abilities were tested using the comprehensive aphasia test (CAT) (Swinburn et al., 2005). The test consists of a number of batteries of tests, including tests of cognitive and language functions and a disability questionnaire. The tests of language function are also divided into those that examine language functions at single-word level, and those that examine language functions at sentence-level. This paper will focus on the patients' performance on 8 single-word language function tests;

1.) Word reading

2.) Non-word reading

3.) Object naming

4.) Word repetition

5.) Non-word repetition

6.) Dictation

7.) Written comprehension

8.) Auditory comprehension

The patients' raw score were scaled before being entered into the analyses. The scaled scores where calculated by dividing the mean centred scores by the standard deviation, and squaring the result. This allows the scores to be grouped on a common scale of difficulty, making direct comparison of one regressor against another possible.

2.3 MR data acquisition

Focal gray and white matter density was estimated on the basis of T1-weighted anatomical whole brain images acquired via a Siemens 1.5 Sonata magnetic resonance imaging (MRI) scanner (Siemens Medical Systems, Erlangen, Germany). A T1-weighted three dimensional (3D) MDEFT (modified driven equilibrium Fourier transform) sequence (Deichmann et al., 2004) was used to acquire 176 sagittal partitions with an image matrix of 256_224 yielding a final resolution of $1mm^3$ [repetition time (TR)/echo time (TE)/ inversion time (TI), 12.24/ 3.56/ 530 ms]. The same scanner parameters and scanner hardware were used for the acquisition of all anatomical volumes.

2.4 MR data processing

Structural images were preprocessed with Statistical Parametric Mapping software running under Matlab 6.5 (MathWorks, Natick, MA). The images were segmented into gray and white matter images using the unified segmentation algorithm, a generative model that combines tissue segmentation, bias correction and spatial normalization in the inversion of a single unified model. Estimating the model parameters (to give a maximum a-posteriori solution) involves alternating among classification, bias correction and registration steps. This approach affords better results than serial applications of each component because it accounts for conditional dependencies among the model; i.e., registration and bias correction help the tissue classification, and the tissue classification helps the registration and bias correction. The

resulting gray and white matter images were smoothed with an isotropic kernel of 8 mm at full-width half maximum. This smoothing kernel was chosen to compensate for the inexact nature of spatial normalization and to maximize the chance that regional effects are expressed at a spatial scale in which homologies in structural anatomy exist over subjects. After smoothing, each voxel represents the local average amount of gray or white matter in the region, the size of which is defined by the smoothing kernel.

2.5 MR data analysis: VBM

VBM is a whole-brain, unbiased, semi-automated technique for characterizing regional cerebral differences in structural magnetic resonance images. Statistical analyses were performed on the smoothed gray matter images using the general linear model as implemented in SPM5. The gray matter images for both the healthy controls and patients were entered into a multiple regression model, with images from the healthy controls and patients modelled separately. Using proportional scaling we excluded global signal intensity effects, and linear and nonlinear effects of age were excluded by including them as covariates of no interest across both groups of subjects (patients and controls).

Results are reported from two different statistical analyses. In the first analysis, there was only one behavioural regressor: Word reading score. This analysis identifies all the brain voxels where damage correlates with reading ability irrespective of the level of processing impairment (visual, phonological etc). In the second analysis, the scores from eight behavioural tasks were included (i.e. reading words, reading non-words, object naming, words and non-word repetitions, dictation, written and auditory comprehension). For each task of interest in both analyses, we included both linear and nonlinear effects. .

In the second analysis, there were 5 effects of interest (see Table 1) corresponding to impairments at the level of (1) auditory processing, (2) visual processing, (3) lexical phonological retrieval, (4) sublexical phonological retrieval and (5) verbal short term memory. To identify these effects, we extracted the T statistic from contrasts that weighted tasks that involved the process of interest (e.g. sublexical phonology) while factoring out all other tasks (see Table 1 for a summary of the tasks and processes of interest). To ensure that all 5 effects were independent of one another, we searched for voxels that showed the effect of interest while excluding voxels associated with all other effects. In the SPM software, this involved selecting the contrast of interest (thresholded at $p<0.001$) and then exclusively masking it with all other effects (also thresholded at $p<0.001$). Effects are only reported if the number of voxels at $p<0.001$ survived a correction for multiple comparisons across the whole brain.

(Table 1) Tasks included in each contrast

CAT tests	Visual	Auditory	Lexical Phonological retrieval	Sublexical Phonological retrieval	Phonological short-term memory
Word Reading	✓	✗	✓	✓	✗
Non-word Reading	✓	✗	✗	✓	✗
Object Naming	✓	✗	✓	✗	✗
Word Repetition	✗	✓	✗	✓	✗
Non-word Repetition	✗	✓	✗	✓	✓
Dictation	✗	✓	✓	✓	✓
Written Comprehension	✓	✗	✗	✗	✗
Auditory Comprehension	✗	✓	✗	✗	✗

Table 1. shows the combination of tasks included in each contrast.

Contrasts

1.) **Areas that impair all auditory-related tasks when damaged.**

This contrast focused on the regressors for the 4 auditory tasks (word repetition, non-word repetition, dictation and auditory comprehension) after factoring out the effects of the 4 visual tasks (word reading, non-word reading, object naming, and written comprehension). It identifies the voxels where low scores on auditory tasks correlate with low gray matter density.

2.) **Areas that impair all visually-related tasks when damaged.**

This contrast focused on the regressors for the 4 visual tasks (word reading, non-word reading, object naming, and written comprehension) while factoring out the effects of the 4 auditory tasks (word repetition, non-word repetition, dictation and auditory comprehension). It identifies the voxels where low scores on visual tasks correlate with low gray matter density.

3.) **Areas that impair lexical-phonological retrieval when damaged.**

This contrast focused on the regressors for the tasks that involved lexical phonological retrieval (object naming, word reading and dictation) while factoring out all other effects. It identifies the voxels where low scores on lexical tasks correlate with low gray matter density.

4.) **Areas that impair sublexical-phonology retrieval when damaged.**

This contrast focused on the regressors for the tasks that involved sublexical phonological retrieval (non-words reading, non-words repetition, word reading, word repetition and dictation) while factoring out object naming and the two comprehension tasks. It identifies the voxels where low scores on sublexical tasks correlate with low gray matter density.

Note that the key difference between the contrasts for lexical and sublexical contrasts involved the comparison of object naming (that involves lexical but not sublexical

phonological retrieval), and non-word reading and repetition (that rely on sublexical but not lexical phonological retrieval). Other tasks (word reading and dictation) can be performed by both lexical and sublexical phonological retrieval and they were therefore included in both the lexical and sublexical contrasts. If we had excluded them from one or both contrasts, the multiple regression would factor out the variance of interest associated with them. Thus this multiple regression approach allowed us to maximise sensitivity and selectivity to the processes of interest.

5.) **Areas that impair tasks requiring phonological short term memory when damaged.**

This contrast focused on the regressors for the tasks that placed particularly high demands on phonological short-term memory (dictation and non-words repetition)

Finally, to identify voxels where damage impaired all our tasks of interest, we report the effects of a contrast that included all regressors and then exclusively masked out effects that were selected for the five contrasts detailed above.

Post-hoc analysis

Post-hoc analyses, outside SPM, were performed to provide face validity for the double dissociation in lexical and sublexical processing identified by the multiple regression analysis. The aim was to examine whether the voxels identified by the multiple regression analysis corresponded to the lesion sites of patients with selective difficulty in lexical versus sublexical phonological retrieval.

Patients with more difficulty in lexical versus sublexical phonological retrieval were identified as those who had abnormally low object naming performance but normal repetition and non-word reading abilities. In contrast, patients with more difficulty in sublexical versus lexical

phonological retrieval were identified as those who had normal object naming performance but abnormally poor repetition and non-word reading abilities.

We then examined the structural MRI image for each of these patients at the locations where the multiple regression analysis identified a double dissociation for lexical and sublexical phonological retrieval at the population level.

3. Results

3.1 Behavioural (CAT) scores

The results for 94 patients' performance on CAT single-word language test are shown on Table 1. The table includes each patients' raw and scaled scores, the abnormal cutoffs, mean and standard deviation.

The abnormal cutoffs for each test are as follows;

- Reading words: 61 and below
- Reading non-words : 57 and below
- Object naming: 61 and below
- Word repetition: 56 and below
- Non-word repetition: 52 and below
- Dictation: 59 and below
- Written ccomprehension :54 and below
- Auditory comprehension: 52 and below

The scaled scores are the ones that were entered into the multiple regression analysis. This allows the test scores to be on a common scale, making direct comparison possible. As mentioned in the previous section, the scaled scores were calculated by dividing the mean centred scores by the standard deviation, and squaring the result (mean centre = each test score minus the mean).

As shown in the table, there is much variability in the performance across patients.

(Table 2) Raw Data

Number	Word Reading		Non-word Reading		Object Naming		Word Repetition		Non-word Repetition		Dictation		Written Comprehension		Auditory Comprehension	
	raw	scaled	raw	scaled	raw	scaled	Raw	scaled	raw	scaled	raw	scaled	raw	scaled	Raw	scaled
1045	62	0.04	61	0.123	74	1.04	65	0.794	67	0.904	68	0.861	59	0.058	58	0.029
1069	69	0.725	68	0.779	74	1.04	65	0.794	46	-1.417	68	0.861	65	0.928	53	-0.731
1240	49	-1.232	40	-1.845	53	-1.031	45	-1.619	38	-2.301	59	-0.171	53	-0.812	60	0.333
1264	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	55	-0.522	58	0.029
1307	69	0.725	68	0.779	70	0.646	57	-0.171	49	-1.085	61	0.058	65	0.928	65	1.093
1356	58	-0.351	49	-1.001	66	0.251	65	0.794	49	-1.085	49	-1.318	65	0.928	65	1.093
1819	69	0.725	64	0.404	57	-0.636	65	0.794	67	0.904	57	-0.401	49	-1.391	58	0.029
2913	69	0.725	68	0.779	66	0.251	65	0.794	58	-0.091	68	0.861	65	0.928	65	1.093
3143	61	-0.058	61	0.123	60	-0.34	51	-0.895	51	-0.864	68	0.861	55	-0.522	51	-1.035
3146	53	-0.84	49	-1.001	50	-1.327	52	-0.775	58	-0.091	49	-1.318	65	0.928	51	-1.035
3228	38	-2.308	40	-1.845	44	-1.918	43	-1.86	46	-1.417	44	-1.892	51	-1.101	53	-0.731
3280	53	-0.84	49	-1.001	58	-0.538	50	-1.016	46	-1.417	53	-0.859	51	-1.101	60	0.333
3853	38	-2.308	40	-1.845	44	-1.918	41	-2.101	38	-2.301	44	-1.892	55	-0.522	46	-1.795
4092	62	0.04	68	0.779	74	1.04	52	-0.775	53	-0.643	63	0.287	65	0.928	53	-0.731
4111	69	0.725	68	0.779	66	0.251	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
4252	69	0.725	68	0.779	64	0.054	65	0.794	67	0.904	68	0.861	55	-0.522	58	0.029
4351	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093

4466	69	0.725	68	0.779	70	0.646	57	-0.171	53	-0.643	63	0.287	65	0.928	60	0.333
4514	69	0.725	68	0.779	66	0.251	60	0.19	67	0.904	68	0.861	65	0.928	65	1.093
4538	38	-2.308	40	-1.845	47	-1.623	49	-1.136	58	-0.091	38	-2.58	44	-2.116	47	-1.643
4633	69	0.725	61	0.123	64	0.054	65	0.794	67	0.904	68	0.861	65	0.928	55	-0.427
4646	69	0.725	64	0.404	62	-0.143	65	0.794	67	0.904	63	0.287	55	-0.522	49	-1.339
4674	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
4682	69	0.725	68	0.779	62	-0.143	65	0.794	53	-0.643	68	0.861	53	-0.812	49	-1.339
4691	69	0.725	68	0.779	74	1.04	65	0.794	53	-0.643	68	0.861	65	0.928	60	0.333
4707	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	59	-0.171	65	0.928	65	1.093
4744	69	0.725	61	0.123	66	0.251	57	-0.171	58	-0.091	61	0.058	65	0.928	65	1.093
4758	57	-0.449	49	-1.001	52	-1.129	65	0.794	58	-0.091	46	-1.662	55	-0.522	49	-1.339
4764	38	-2.308	40	-1.845	43	-2.017	41	-2.101	38	-2.301	46	-1.662	49	-1.391	41	-2.555
4769	51	-1.036	40	-1.845	52	-1.129	56	-0.292	67	0.904	50	-1.204	55	-0.522	53	-0.731
4777	57	-0.449	68	0.779	60	-0.34	52	-0.775	58	-0.091	57	-0.401	55	-0.522	65	1.093
4791	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
4807	62	0.04	68	0.779	64	0.054	65	0.794	67	0.904	61	0.058	55	-0.522	65	1.093
4840	69	0.725	68	0.779	61	-0.242	65	0.794	58	-0.091	63	0.287	65	0.928	65	1.093
4854	69	0.725	68	0.779	66	0.251	57	-0.171	67	0.904	68	0.861	65	0.928	60	0.333
4876	69	0.725	68	0.779	66	0.251	65	0.794	67	0.904	52	-0.974	65	0.928	65	1.093
4962	69	0.725	68	0.779	70	0.646	57	-0.171	67	0.904	68	0.861	55	-0.522	60	0.333
4977	38	-2.308	40	-1.845	37	-2.609	35	-2.825	46	-1.417	38	-2.58	49	-1.391	55	-0.427
4994	69	0.725	68	0.779	74	1.04	55	-0.413	53	-0.643	68	0.861	65	0.928	65	1.093

5011	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	63	0.287	65	0.928	60	0.333
5063	38	-2.308	40	-1.845	37	-2.609	35	-2.825	38	-2.301	44	-1.892	49	-1.391	49	-1.339
5071	69	0.725	68	0.779	74	1.04	56	-0.292	53	-0.643	68	0.861	65	0.928	65	1.093
5077	55	-0.645	49	-1.001	61	-0.242	65	0.794	67	0.904	68	0.861	49	-1.391	65	1.093
5078	69	0.725	64	0.404	74	1.04	57	-0.171	67	0.904	68	0.861	55	-0.522	58	0.029
5095	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
5109	53	-0.84	58	-0.158	55	-0.834	48	-1.257	49	-1.085	63	0.287	49	-1.391	49	-1.339
5132	69	0.725	68	0.779	66	0.251	65	0.794	58	-0.091	68	0.861	65	0.928	65	1.093
5177	69	0.725	68	0.779	66	0.251	65	0.794	67	0.904	68	0.861	59	0.058	58	0.029
5219	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
5252	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
5276	60	-0.156	68	0.779	61	-0.242	65	0.794	67	0.904	63	0.287	53	-0.812	51	-1.035
5291	69	0.725	61	0.123	74	1.04	65	0.794	67	0.904	57	-0.401	51	-1.101	65	1.093
5359	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
5396	62	0.04	61	0.123	66	0.251	60	0.19	67	0.904	57	-0.401	53	-0.812	55	-0.427
5410	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	58	0.029
5433	38	-2.308	40	-1.845	37	-2.609	35	-2.825	38	-2.301	38	-2.58	39	-2.841	42	-2.403
5461	69	0.725	68	0.779	70	0.646	57	-0.171	53	-0.643	63	0.287	65	0.928	55	-0.427
5484	69	0.725	68	0.779	66	0.251	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
5499	69	0.725	68	0.779	74	1.04	65	0.794	62	0.351	68	0.861	53	-0.812	60	0.333
5523	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	63	0.287	59	0.058	65	1.093
5525	69	0.725	61	0.123	74	1.04	65	0.794	67	0.904	59	-0.171	65	0.928	60	0.333

5535	55	-0.645	56	-0.345	55	-0.834	65	0.794	67	0.904	59	-0.171	49	-1.391	55	-0.427
5552	45	-1.623	40	-1.845	46	-1.721	43	-1.86	38	-2.301	61	0.058	65	0.928	53	-0.731
6000	69	0.725	68	0.779	74	1.04	60	0.19	67	0.904	68	0.861	65	0.928	58	0.029
6034	64	0.236	68	0.779	70	0.646	60	0.19	67	0.904	68	0.861	65	0.928	65	1.093
6054	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	65	1.093
6076	43	-1.819	40	-1.845	37	-2.609	49	-1.136	49	-1.085	45	-1.777	45	-1.971	46	-1.795
6140	58	-0.351	52	-0.72	59	-0.439	65	0.794	55	-0.422	61	0.058	55	-0.522	55	-0.427
6242	69	0.725	68	0.779	74	1.04	65	0.794	55	-0.422	63	0.287	59	0.058	58	0.029
6257	50	-1.134	49	-1.001	66	0.251	50	-1.016	49	-1.085	59	-0.171	55	-0.522	49	-1.339
6262	60	-0.156	56	-0.345	60	-0.34	60	0.19	55	-0.422	63	0.287	65	0.928	65	1.093
6319	46	-1.525	40	-1.845	54	-0.932	65	0.794	62	0.351	38	-2.58	53	-0.812	60	0.333
6360	69	0.725	68	0.779	66	0.251	65	0.794	58	-0.091	68	0.861	65	0.928	65	1.093
6369	55	-0.645	58	-0.158	59	-0.439	45	-1.619	58	-0.091	55	-0.63	65	0.928	44	-2.099
6377	69	0.725	68	0.779	64	0.054	56	-0.292	58	-0.091	68	0.861	65	0.928	53	-0.731
6383	62	0.04	61	0.123	62	-0.143	65	0.794	58	-0.091	61	0.058	55	-0.522	60	0.333
6393	60	-0.156	56	-0.345	55	-0.834	46	-1.498	44	-1.638	57	-0.401	59	0.058	55	-0.427
6406	69	0.725	68	0.779	60	-0.34	60	0.19	67	0.904	68	0.861	55	-0.522	53	-0.731
6411	69	0.725	68	0.779	70	0.646	65	0.794	67	0.904	63	0.287	59	0.058	60	0.333
6422	61	-0.058	61	0.123	54	-0.932	55	-0.413	53	-0.643	61	0.058	59	0.058	49	-1.339
6428	53	-0.84	54	-0.533	53	-1.031	50	-1.016	58	-0.091	51	-1.089	65	0.928	42	-2.403
6488	69	0.725	68	0.779	62	-0.143	56	-0.292	67	0.904	68	0.861	51	-1.101	58	0.029
6492	69	0.725	68	0.779	74	1.04	65	0.794	58	-0.091	68	0.861	65	0.928	60	0.333

6552	53	-0.84	51	-0.814	64	0.054	46	-1.498	53	-0.643	59	-0.171	59	0.058	55	-0.427
6606	69	0.725	68	0.779	66	0.251	65	0.794	62	0.351	61	0.058	55	-0.522	58	0.029
6673	49	-1.232	40	-1.845	57	-0.636	55	-0.413	49	-1.085	49	-1.318	43	-2.261	53	-0.731
6707	55	-0.645	40	-1.845	50	-1.327	57	-0.171	49	-1.085	45	-1.777	53	-0.812	65	1.093
6722	48	-1.33	40	-1.845	74	1.04	52	-0.775	58	-0.091	52	-0.974	55	-0.522	53	-0.731
6765	38	-2.308	40	-1.845	57	-0.636	50	-1.016	49	-1.085	50	-1.204	42	-2.406	47	-1.643
6805	69	0.725	61	0.123	64	0.054	60	0.19	67	0.904	68	0.861	65	0.928	58	0.029
6808	69	0.725	68	0.779	61	-0.242	65	0.794	67	0.904	68	0.861	59	0.058	58	0.029
6818	69	0.725	68	0.779	74	1.04	65	0.794	67	0.904	68	0.861	65	0.928	60	0.333
6821	69	0.725	56	-0.345	59	-0.439	65	0.794	67	0.904	57	-0.401	65	0.928	60	0.333
56864	49	-1.232	49	-1.001	61	-0.242	48	-1.257	48	-1.196	54	-0.745	51	-1.101	60	0.333
Mean	61.511		59.72		63.34		58.44		58.79		60.53		58.6		57.79	
SD	10.243		10.72		10.13		8.338		9.096		8.76		6.94		6.614	
Abnormal Cufoffs (below)	**61**		**57**		**61**		**56**		**52**		**59**		**54**		**52**	

Table 2. The table shows the patients' performance on 8 single-word CAT language tests. The abnormal cutoffs are the score that indicate abnormal performance in those tests. The scaled scores are the values entered into the multiple regression analysis, as they allow a common scale in which the performance can be directly compared.

3.2 Lesion Overlap

Figure 1 shows the lesion overlap map of all 94 patients. This was done to illustrate the variability in lesion sites in our sample, but was not used in the lesion-deficit analysis.

(Figure 1) Lesion Overlap

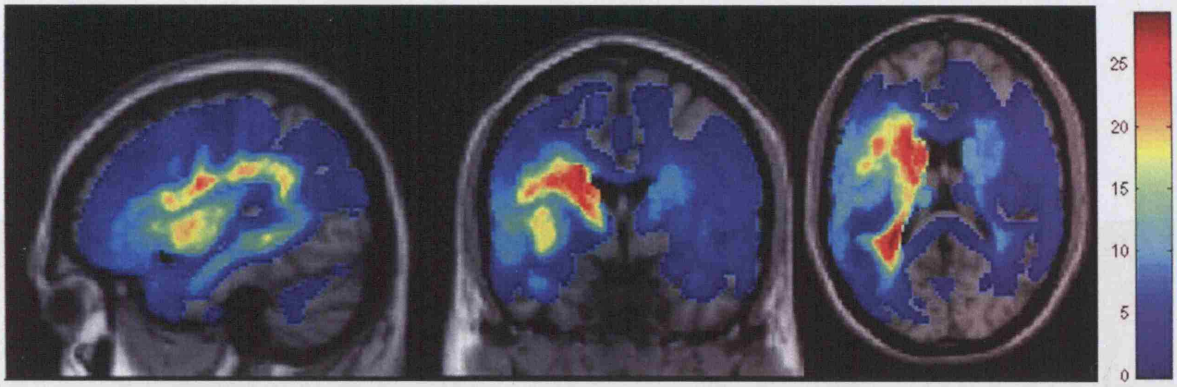

Figure 1. shows the lesion overlap map. The map shows the location of the lesions across 94 patients. The colour bar indicates the number of patients that have a lesion in that location.

3.3 Multiple regression results

The results of multiple regressions are summarised in Table 2. The table shows the summary of the coordinates of low gray matter density in relation to the effects of interest (e.g. poor performance in visually-dependent tasks). The table also contains the z-score which indicates level of significance, and the size of cluster. Each effect of interest will be discussed individually in the following sections.

(Table 3) Multiple regression results

Effect of interest	Area of low gray matter density	Coordinates	Z-score	Size of cluster (voxel)
Poor Visual-tasks				
	Occipital cortex	(-36 -83 26)	4.6	113
		(-34 -88 16)	4.2	
Poor auditory tasks				
	Superior temporal	(-62 -12 -6)	4.2	967
		(-64 -28 4)	4.1	
		(-46 -36 20)	4	
		(-62 -36 20)	3.9	
Poor lexical phonological retrieval				
	Left inferior frontal	(-46 38 -6)	4.1	296
		(-50 36 6)	3.8	
		(-44 34 -14)	3.6	

	Left Anterior insula	(-30 14 -14)	4.1	228
		(-30 22 2)	3.7	
	Left head of caudate	(-12 16 -4)	4.6	184
	Right cerebellum	(32 -80 -38)	4.1	506
		(22 -80 -46)	4	
		(30 -80 -26)	3.9	
		(36 -46 -26)	3.8	
		(42 -62 -26)	3.8	
Poor sublexical phonology				
	Left posterior insula	(-34 -24 6)	4.5	164
		(-34 -26 16)	4.2	
		(-36 -26 20)	3.7	
	Left thalamus	(-10 -28 8)	3.9	392
		(-6 -22 12)	3.8	
Poor Verbal short-term memory				
	supramarginal gyrus	(-62 -34 32)	4.3	501
		(-56 -22 26)	4.2	
		(-48 -26 48)	3.8	
		(-52 -36 46)	3.6	
All else	Posterior frontal-anterior temporal	(-42 -6 0)	5.7	2486
		(-44 6 0)	5.6	

		(-40 -4 -8)	5.4	
		(-50 2 0)	5.4	
		(-48 10 34)	5.4	
		(-56 12 14)	5.2	
		(-50 24 4)	5.1	
		(-38 6 8)	5.1	
		(-52 6 -6)	5	
		(14 6 14)	4.9	

Table 3. A table summarising the results of the effects of interest from the multiple regression analyses. The z-scores show how many standard deviations away from the mean the values are. The size of cluster indicates the extent (size) at each coordinates. Effects were significant after correction for multiple comparisons across the whole brain in either extent or height.

3.3.1 Areas that impair reading ability when damaged

Figure 2 shows all the areas in the brain that when damaged affect reading ability. The results show reading is heavily left-lateralised and that the following regions contribute to reading ability; posterior frontal, motor areas, anterior temporal and superior temporal cortices, posterior temporal cortex, supramarginal cortex, insula, caudate nucleus, thalamus, and cerebellum. These areas are not unique for reading, but are involved in the various processes that underlie reading ability (e.g. ability to see-visual cortex etc.)

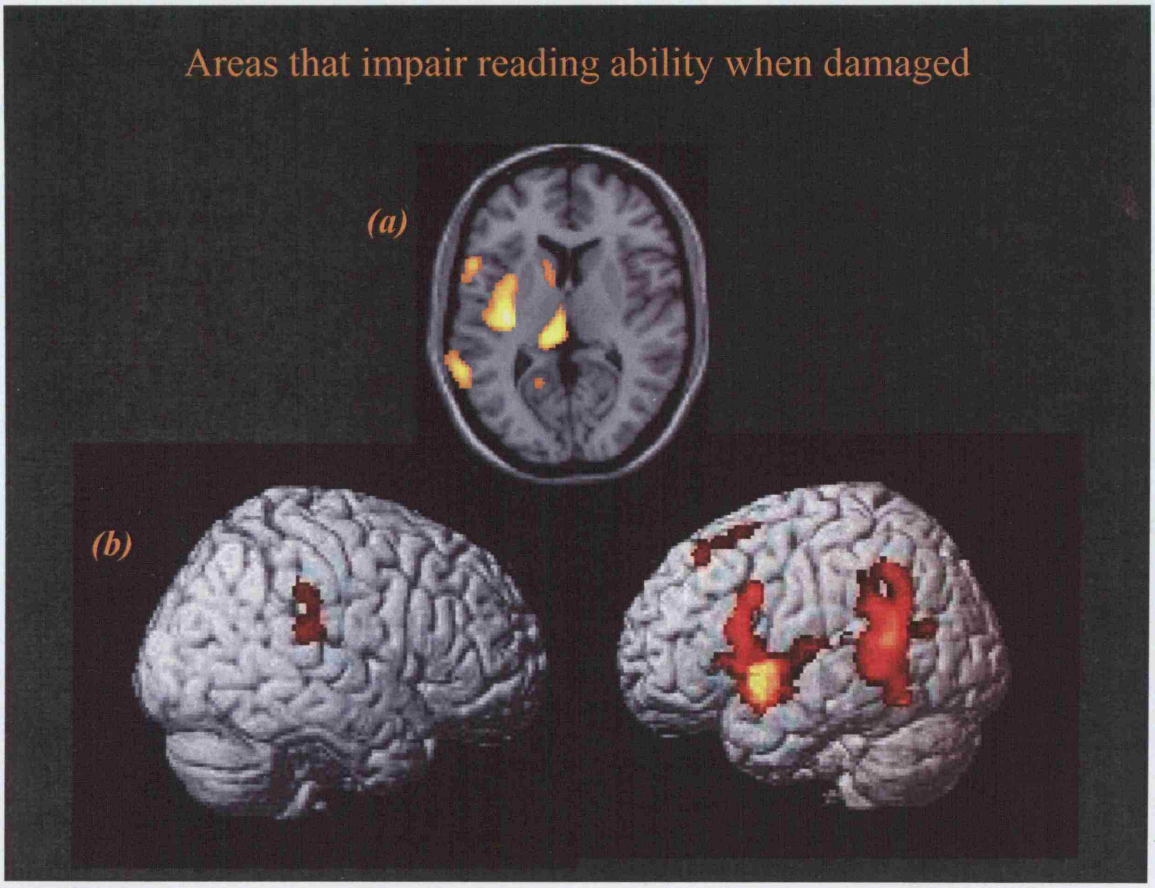

Figure 2. *(a) and (b)* highlight all the regions of the brain that when damaged impair reading ability. *(a)* horizontal section through the brain showing insula temporal, caudate, thalamus and cerebellum. (b) shows a surface rendering of all effects.

3.3.2 Areas that impair visual-tasks, auditory-tasks, and phonological short-term memory tasks when damaged

Figure 2 shows the areas where damage differentially impaired visual versus auditory tasks. Visual tasks included word reading, non-word reading, object naming, and written comprehension (4 tasks in total), while auditory tasks included word and non-word repetition, dictation and auditory comprehension.

The results of the multiple regression analyses shows that damage to the left dorsal occipital lobe (shown in pink), impairs visual tasks more than auditory tasks, while damage to the left superior temporal lobe impairs auditory tasks more than visual tasks. These results are as expected and thus support analytical approach.

The supramarginal gyrus shown in purple (figure 2) indicates the regions which when damaged impair phonological short-term memory tasks more than others. It is interesting to see the dissociation between auditory-tasks, and phonological short-term memory tasks in the superior temporal and supramarginal areas respectively. This is consistent with findings in the literature (Buchsbaum and D'Esposito, 2008; Henson et al., 2000; Paulesu et al., 1993).

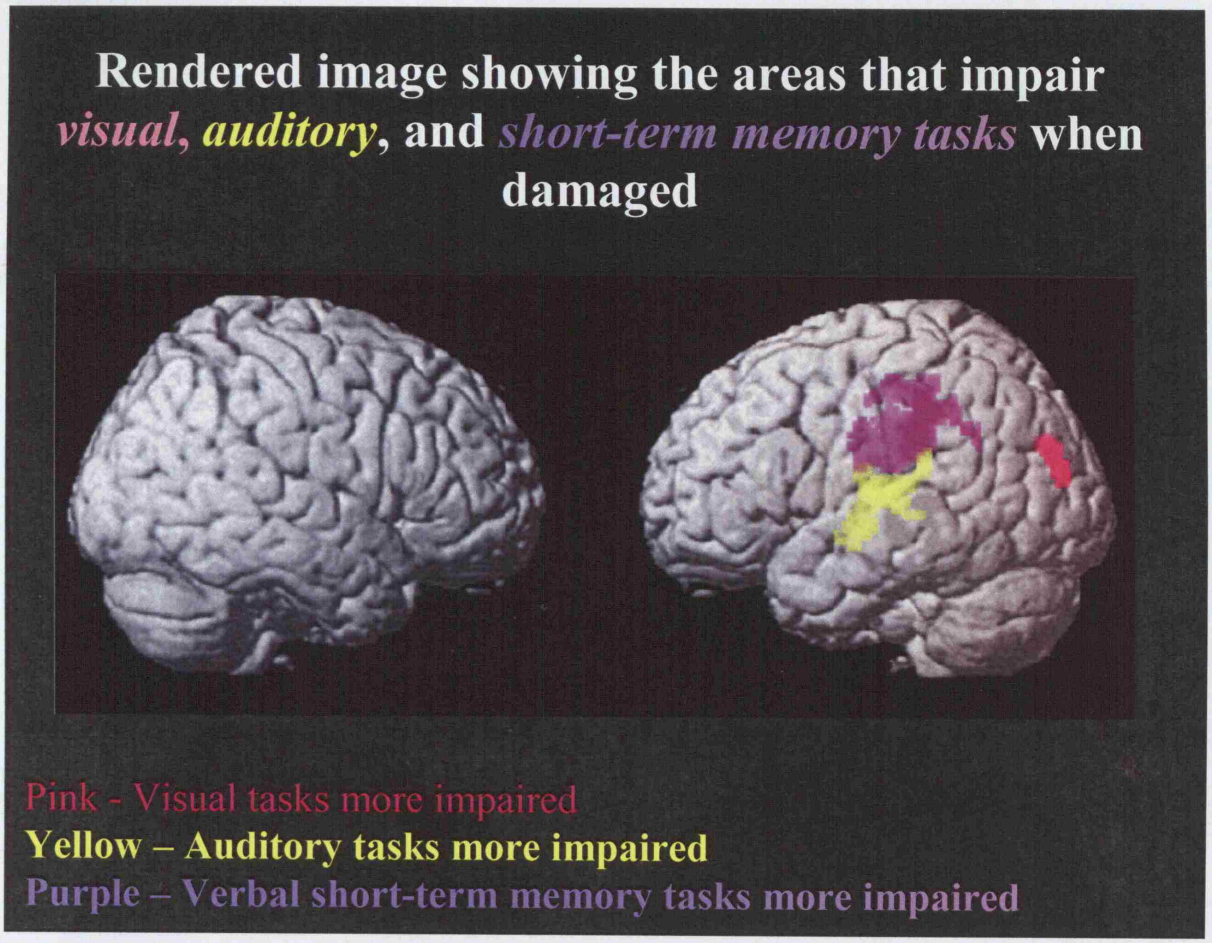

Figure 3. Rendered image of the areas where damage impairs visual tasks (pink), auditory tasks (yellow), and tasks dependent on verbal short-term memory (purple).

3.3.3 Areas that impair lexical phonology vs. sublexical phonology when damaged

This contrast identifies the brain regions involved in lexical phonological retrieval (green), and sublexical phonology (blue) (see Figure 3 and Figure 4).

For lexical phonology, multiple regression identifies 4 distinct brain regions: inferior frontal (frontal orbitalis), left anterior insula, left head of caudate, and right cerebellum. For sublexical phonology, two regions were identified in the posterior insula, and left thalamus (coordinates of which are summarised in Table 2.). This functional dissociation between the anterior and posterior insula in lexical and sublexical phonology respectively is particularly fascinating.

Further illustration of the brain areas involved in lexical and sublexical phonological retrieval can be seen in Figure 4. The figure shows horizontal sections showing the brain regions mentioned above.

3.3.4 Areas that impairs all other language processes not examined here when damaged

This contrast identifies the brain regions where damage impairs the ability to perform all tasks or combinations of tasks not tested in the above analyses. The areas are those that remain when the effects of all other conditions have been subtracted. They are shown in red in Figures 3 and 4, and comprise frontal regions (extending into the motor cortex), and superior temporal regions.

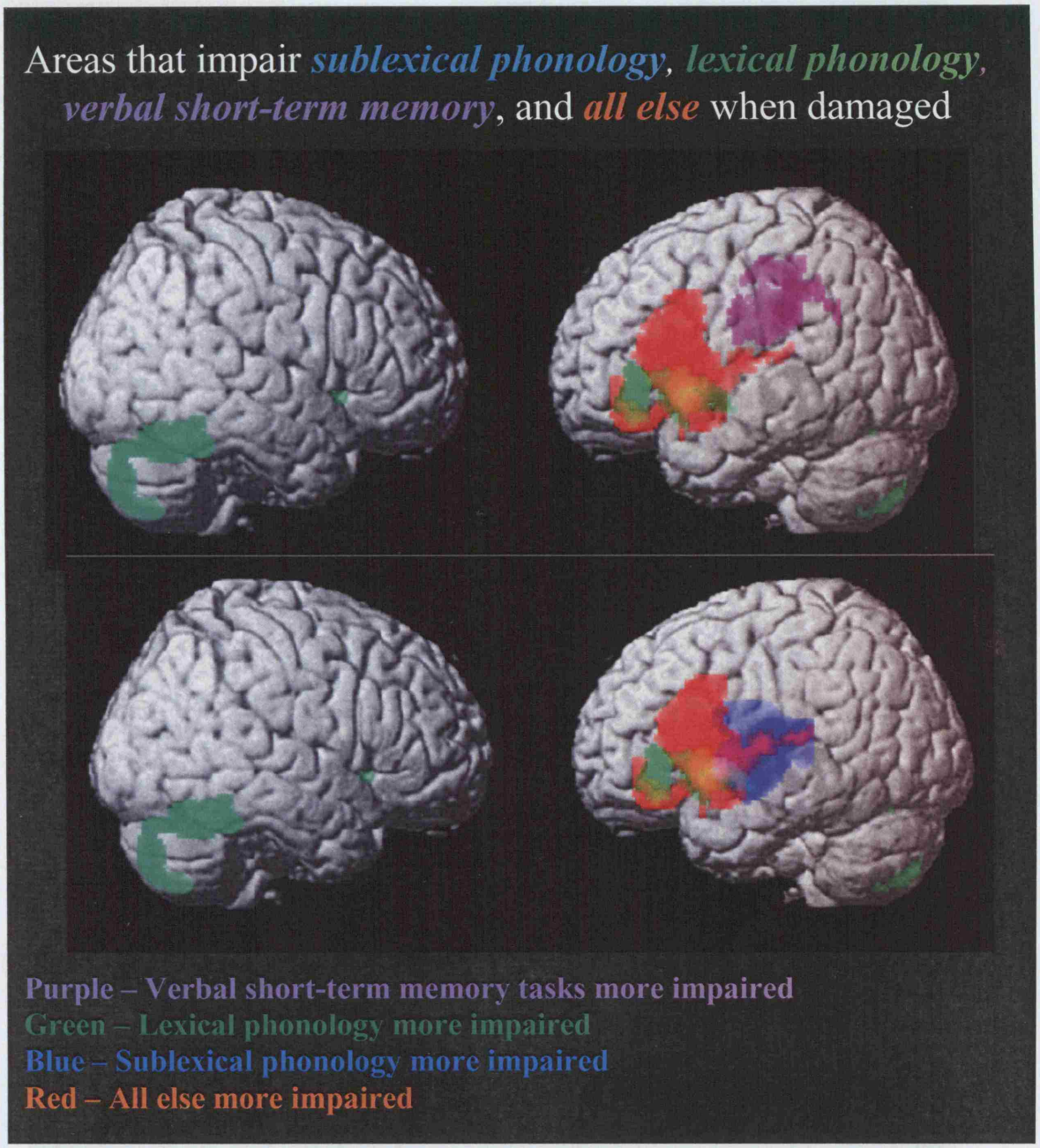

Figure 4. Rendered images of the areas where damage impairs short-term memory tasks (purple), lexical phonology (green), sublexical phonology (blue), and all else not identified in the above (red).

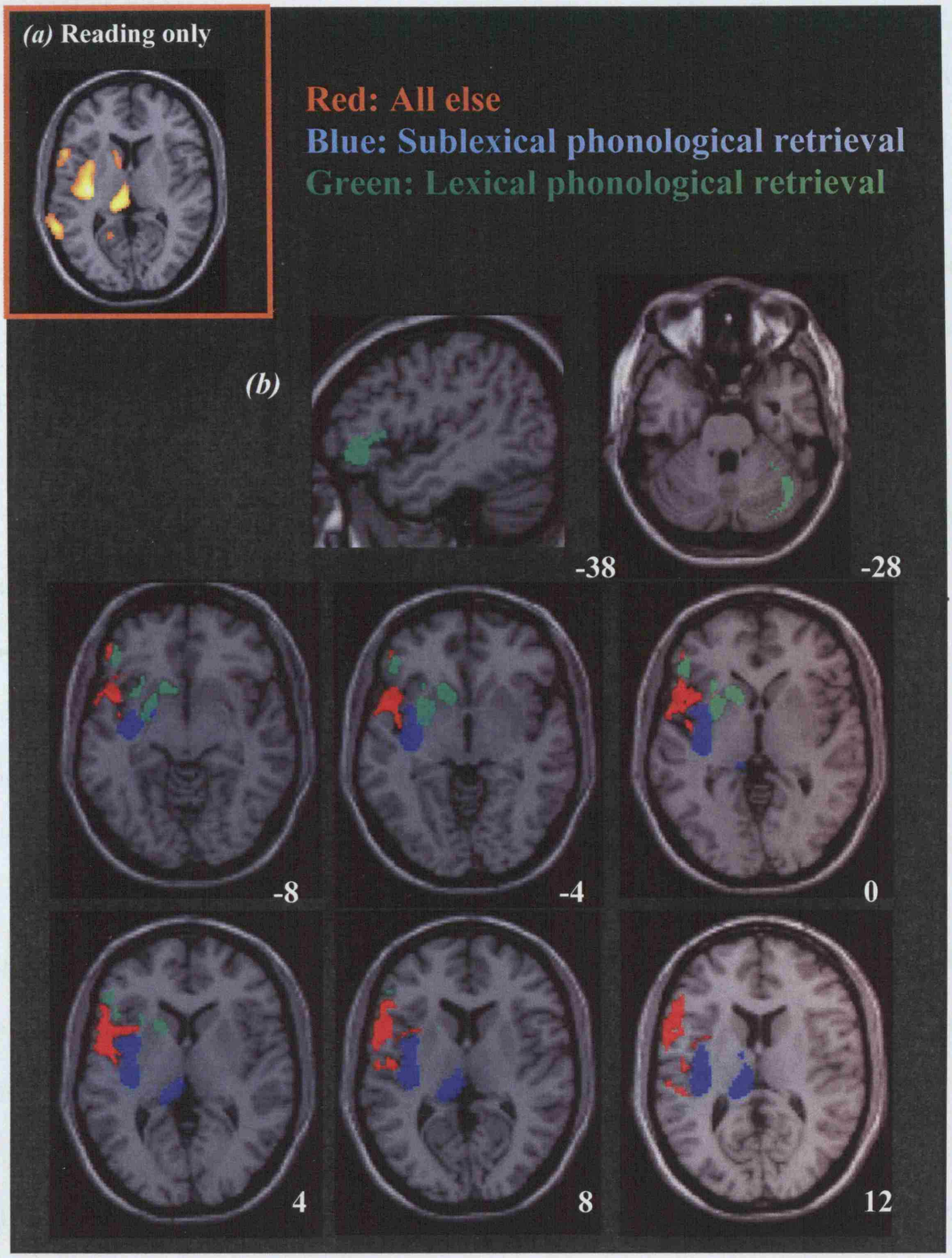

Figure 5. *(a)* Cross section showing the regions associated with reading ability in analysis 1. *(b)* sections showing the areas that when damaged impair lexical phonological retrieval (green), sublexical phonological retrieval (blue), and all other language processes (red). The regions indicated in *(b)* are almost identical to those seen in *(a)*, but illustrate how the different areas are associated with different functions, illustrating how many processes underlie the ability to read (e.g. lexical phonology and sublexical phonology).

3.4 Post-hoc analysis

The post hoc analysis identified 4 patients who were good at object naming, but poor at word and non-word repetition (patients 6488, 56864, 6552), and 3 patients who were poor at object naming, but good at word and non-word repetition (patients 5535 4758, 4769). The former are examples of patients with the greatest dissociation between sublexical phonology, which was impaired and lexical phonology, which was intact. The latter show the reverse dissociation (poorer lexical than sublexical phonology.)

The structural MRI images of the four patients with more impaired sublexical phonological retrieval are shown in Figures 6 and 7.

6488: had focal damage in the left thalamus

6552: had a lesion in the posterior insula

56864: had white matter abnormality near the posterior insula and the thalamus that was associated with reduced grey matter in both regions.

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Interestingly, the fourth patient (patient 6257) with a selective impairiment in sublexical phonology had extensive damage that included the right posterior insula, the homologue of the area identified in the VBM analysis (see Figure 6).

The structural MRI images of the two patients with more impaired lexical phonological retrieval are shown at the bottom of Figure 4. Both patients (5535 and 4758) had large lesions in the ventral inferior frontal cortex that extended into the left anterior insula and caudate. Thus, this post hoc analysis provides important information because it indicates that we can not dissociate whether the language impairment was caused by damage to the inferior frontal or anterior insula or both.

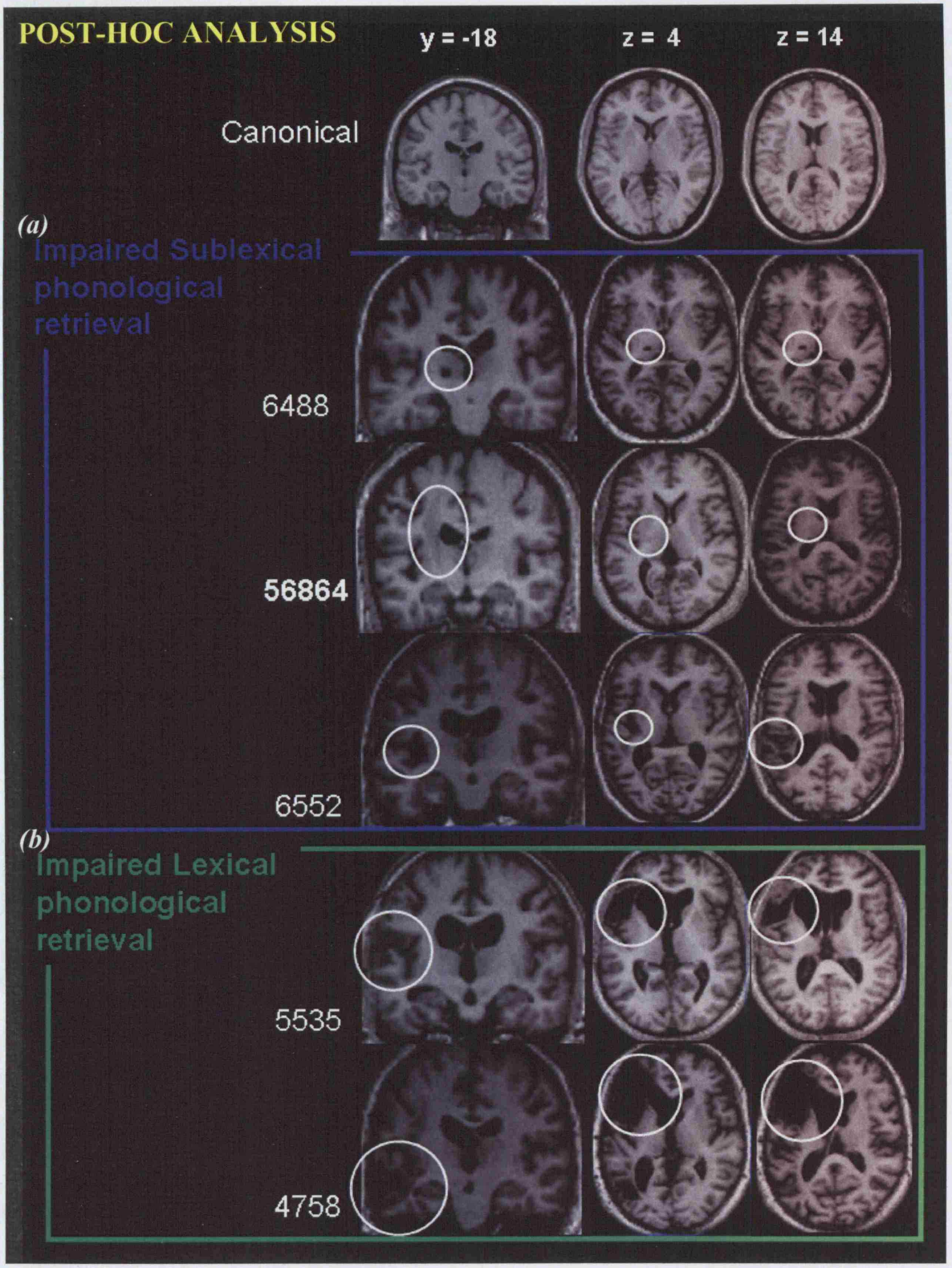

Figure 6. summarises the findings of the post hoc analysis. *(a)* Three patients (6488, 56864, 6552) had a selective impairment in sublexical phonology (good naming, poor repetition). These patients had damage to components of the sublexical phonological retrieval system as

identified by VBM analysis (i.e. the thalamus and posterior insula). Patient 56864 does not actually have a lesion in the gray matter, but has a white matter abnormality between the posterior insula and the thalamus (indicated by the white circle). *(b)* two patients (5535, 4758) had selective impairments in lexical phonological (poor naming, good repetition). These patients have large lesions in the left inferior frontal cortex, extending into the anterior insula.

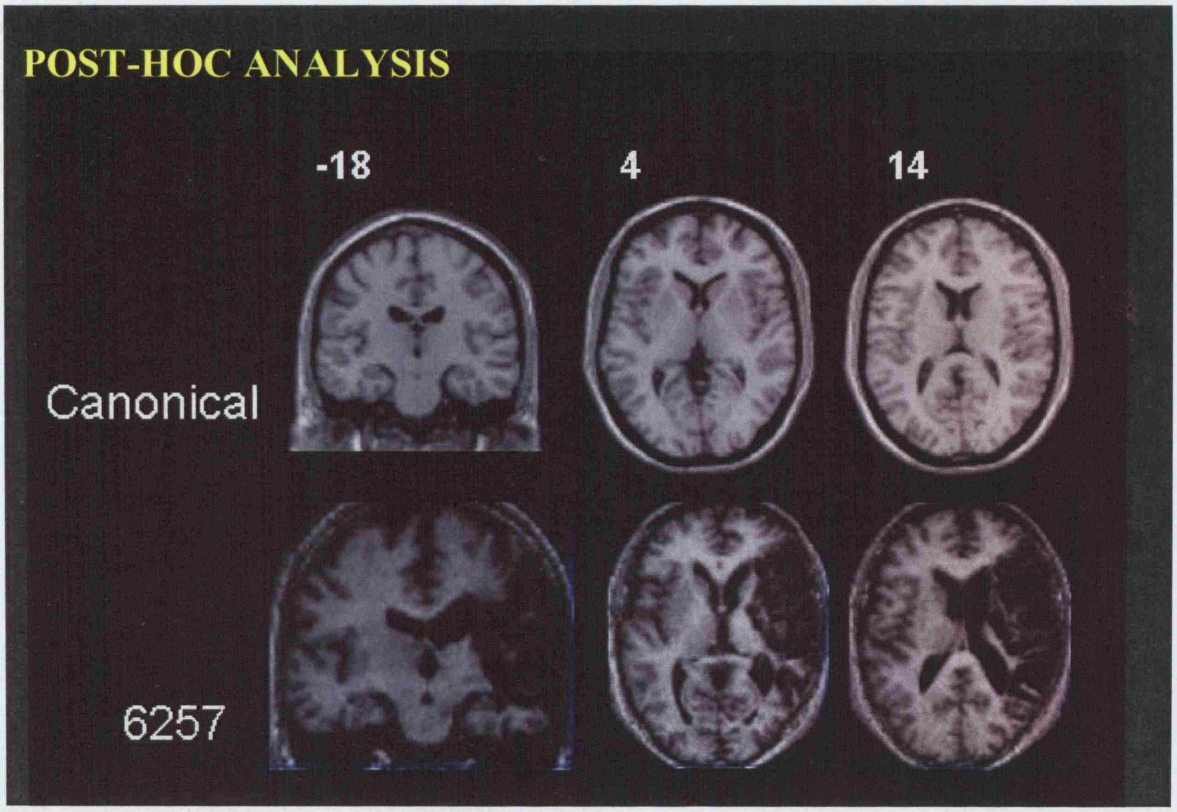

Figure 7. shows the structural brain image of the fourth patient (6257) with a selective impairment in sublexical phonology (good naming, poor repetition). Interestingly, the patient had damage to the homologue areas identified in the VBM analysis. The patient had extensive right-sided damage that included the posterior insula.

4. Discussion

4.1 Summary of results

The aim of this study was to examine the extent to which lesion site can predict language performance after stroke. In summary, the results show that acquired speech production deficits were most likely following lesions to any of the following regions: frontal orbitalis, the insula (anterior and posterior), caudate, thalamus, and cerebellum. More specifically, lexical phonological retrieval is more impaired if the damage is restricted to the left ventral frontal areas extending into the anterior insula, and caudate, while sublexical phonological retrieval is more impaired if damage is restricted to the left posterior insula and left thalamus. The results also showed that phonological short-term memory is dependent upon the left supramarginal gyrus, consistent with many previous functional imaging studies of healthy subjects. Finally, once these task-specific effects had been accounted for, there remains a large area of posterior frontal cortex where damage impairs performance in all eight speech production/ semantic tasks.

The results in relation to previous findings

The VBM analysis showed that lexical and sublexical speech production depends on different anatomical systems. The analysis also supports several previous findings including the role of the anterior insula in speech production (Ackermann and Riecker, 2004; Blank et al., 2002; Dronkers, 1996; Wise et al., 1999), supramarginal gyrus in phonological short-term memory (Baddeley, 1968; Baddeley, 2003; Buchsbaum and D'Esposito, 2008; Henson et al., 2000; Paulesu et al., 1993), the role of the thalamus (De Witte et al., 2006; Murdoch, 2001), and the role of the cerebellum in language (Ackermann et al., 2007; Crosson, 1999; De Smet et al., 2007; Vlachos et al., 2007).

4.2 Lexical phonological retrieval: anterior insula and ventral inferior frontal cortex

Many clinical and functional studies have shown that the left anterior insula is involved in articulatory planning. In 1996 Dronkers investigated the brain areas involved in speech articulation by studying the brains of 25 stroke patients with apraxia and 19 stroke patients without apraxia (Dronkers, 1996). When lesion overlap of the CT and MRI scans was done in the two groups, a double dissociation was found; all patients with articulatory planning deficits had lesions in the anterior insula, while none of patients without apraxia had lesions in the insula (Dronkers, 1996). A PET imaging study investigated the brain areas involved in articulation in different speech tasks in healthy subjects and also found the insula to be significantly involved in articulation (Wise et al., 1999). This study involved the participants performing one of three different tasks; repeating single words, listening to single words, anticipating repeating or listening. The results of the study showed that Broca's area was not activated during repetition of single words, instead a region in the basal ganglia and the left anterior insula was activated. The insula also appeared to show a conjunction of activity with the premotor cortex. In addition articulation also appears to modulate the response to hearing in the left temporal cortex. The authors concluded the left anterior insula and the premotor cortex are involved in making an articulatory plan.

Most imaging studies of speech production have concentrated on single word production to reduce other confounding factors such as head-movements, however, some studies have looked at longer utterances. An example of this was a PET study looking at brain regions active during propositional speech and non-propositional speech (e.g. counting and reciting) (Blank et al., 2002). The study was designed to examine the brain areas involved in normal communicative speech. The results showed that the areas involved in the motor act of articulation which is common to both forms of speech were the posterior part of the supratemporal plane, the lateral part of the supratemporal plane, the lateral part of the pars opercularis, and the anterior insula.

Another study that examined conversational speech production was reported by Borovsky and colleagues (Borovsky et al., 2007). The study used VLSM to investigate the lesional correlates of conversation speech production deficits. Aspects of conversation speech such as fluency, grammatical complexity and lexical diversity were examined. The results of the study showed that deficits in production of both fluency and grammatical complexity were associated with lesions in the motor and somatosensory cortex, which included the anterior insula and the inferior frontal gyrus, while the production of lexically diverse speech correlated with posterior superior temporal and medial temporal gyrus.

In summary, apraxia of speech has been shown to be caused by lesions in the anterior insula (Dronkers, 1996). Because apraxia of speech does not involve impairment of the motor tract, it is thus considered to be a deficit at the level of articulatory and phonatory planning. The VBM we conducted analyses did not distinguish between articulatory and phonatory planning. From the results of the post hoc analysis, we see that most patients who had damage to the left anterior insula, in fact had large lesions that extended into the left ventral inferior frontal cortex. Thus, although it is clear that the left anterior insula is crucially involved in speech production, its precise role and the effects of damage to this area cannot be determined fully in this present study.

The inferior frontal cortex has been shown to be crucially important in language processing. Lesion studies have shown that damage to this area results in speech production deficits that can also include phonemic disorder, impaired syntax, lexical access and word finding. The inferior frontal gyrus can be subdivided into 3 parts; pars orbitalis, pars triangularis, and pars opercularis, with the classical Broca's area in the pars triangularis and pars opercularis (Dronkers et al., 2007). There is evidence that each sub-region of the inferior frontal gyrus is specialised for different types of tasks. Neuroimaging and neuropsychological studies have

shown that the left inferior frontal cortex is involved in both semantic and phonological processing. Neuropsychological studies have shown that selective damage to different parts of the inferior frontal cortex can result in different impaired process. Tauber and colleagues suggested that damage to different parts of the inferior frontal cortex and their projections can result in at least five different nonfluent aphasic disorders (Taubner et al., 1999). An imaging study reported by Demonet and colleagues contrasted a phonological (phonemes) task with a semantic (words) task. The result showed phonological processing activated the left inferior frontal gyrus, particularly Broca's area, in addition to activating the superior temporal gyrus (Demonet et al., 1992). Poldrack and colleagues (Poldrack et al., 1999) examined functional specialisation within the inferior frontal cortex using fMRI. From their study, phonological processing of words and non-words was associated with left dorsal inferior frontal gyrus, while semantic processing was associated with the left ventral inferior frontal gyrus (Poldrack et al., 1999). Other studies have also found that different parts of the inferior frontal cortex are specialised for semantic and phonological processing and speech production tasks (Buckner et al., 1995; Damasio et al., 1996; Fiez, 1997).

The results of the current VBM analysis showed that the ventral left inferior frontal cortex, specifically the frontal orbitalis, is part of a lexical phonological retrieval network but this system also included the anterior insula, the caudate nucleus and the right cerebellum as mentioned previously. The consistency of the current results with previous functional imaging studies supports the findings that the ventral inferior frontal cortex is involved in lexical-semantic processing as mentioned above. However, since the analysis reported here did not look at semantic processing specifically, we cannot distinguish the semantic components from the lexical phonology components within the lexical phonological retrieval network. This is because the regressors that were included in the lexical phonology contrast also contained strong semantic components (e.g. word-reading, and object-naming).

4.3 Sublexical phonological retrieval: posterior insula and thalamus

The VBM analysis showed that the left posterior insula and the left thalamus are part of a sublexical phonological retrieval network. In the post hoc analysis, four patients had impaired sublexical phonological retrieval ability: one had focal damage in the left thalamus, one had a lesion in the posterior insula, one had abnormal white matter between the thalamus and posterior insula and the fourth had damage to the right insula. Interestingly, previous studies have shown little evidence for the role of the posterior insula in language (Ackermann and Riecker, 2004; Cereda et al., 2002). Therefore this dissociated function between the anterior insula (in lexical phonology), and posterior insula (in sublexical phonology) appears to be a novel finding. Further studies are now needed to confirm the precise contribution of the posterior insula in language. The prediction from the current study is that the posterior insula is involved in sublexical phonology.

As mentioned previously, our results highlighted the role of the left thalamus in language. Lesions of the subcortical regions including the thalamus have long been shown to cause language impairment (Bruce et al., 2004; Crosson, 1999; De Witte et al., 2006; Murdoch, 2001). Most previous studies investigating the role of the thalamus in language have been done on patients suffering from *thalamic aphasia,* a speech disorder acquired following injuries to the thalamus. Thalamic aphasias have been associated with many behavioural symptoms, from the more motor aspects such as dysarthria to the more cognitive aspects such as anomia, impaired comprehension, general dysfluency, and paraphrasias (Bruce et al., 2004; Crosson, 1999; De Witte et al., 2006; Johnson and Ojemann, 2000; Kuljic-Obradovic, 2003; Murdoch, 2001). Although there are many symptoms associated with thalamic aphasia, most common manifestations are preserved repetition, and impaired naming (Crosson, 1999; De Witte et al., 2006; Kuljic-Obradovic, 2003). However, this is somewhat different from the findings in our

study which showed taht that the left thalamus is part of the sublexical phonological retrieval system and thus damage impaired repetition.

However, it is also believed that different nuclei of the thalamus may be involved in different cognitive processes. Electrical stimulation of the thalamus has been shown to cause language deficits with the precise nature of the language deficit being dependent upon the rostrocaudal location of the stimulation site (Johnson and Ojemann, 2000). Stimulation of the anterior ventrolateral portion resulted in the production of a repeated erroneous word, stimulation of the medial ventrolateral portion resulted in perseveration, while stimulation of the posterior portion and anterior pulvinar resulted in naming deficits. The results from Johnson and Ojemann's study also showed that stimulation of the left thalamus affected short-term memory-tasks, while stimulation during memory input increased recall accuracy, and stimulation during memory output decreased recall errors. Interestingly, stimulation of the same regions of the thalamus also appeared to affect the motor aspect of speech production as well, resulting in slurred speech and problems articulating. The authors proposed that it is possible that the left thalamus may be involved in coordinating the cognitive aspects of language with the motor aspects, a process that is required for voluntary speech. Moreover, stimulation of the thalamus have also been shown to impair mental arithmetic. Since the thalamus seems to be involved in many tasks, the authors proposed that stimulation of the ventrolateral thalamic regions generates a 'specific alerting response' which acts as a gating mechanism that controls the inputs and retrieval of specific items.

Nadeau and Crosson proposed a model called selective engagement in 1997 (Nadeau and Crosson, 1997). According to this model, the thalamus is part of the selective engagement network which also included the frontal lobe, the nucleus reticularis, and the inferior thalamic peduncle. According to Crosson and Nadeau this mechanism selectively engages specific

cortical areas required to perform a particular task, while keeping the other areas in a state of disengagement. However, the authors proposed that deficits in selective engagement mechanism would affect disproportionately the lexical-semantics tasks more than lexical-sublexical processing because lexical-semantics processing is more dependent upon the selective engagement mechanism (Crosson, 1999). Crosson also suggested that different thalamic nuclei are involved in different cognitive processes, and thus the precise symptoms of thalamic aphasia would depend upon the nuclei and the connections affected.

In summary, our result highlighted the role of the thalamus in language. The findings of our study showed that the thalamus is important in sublexical phonological retrieval system, and damage would selectively impair repetition ability. However, as our analyses did not dissociate between different thalamic nuclei, we cannot say if it is true if different thalamic nuclei have different roles in language processing. The fact that our findings exclude the thalamus from naming ability challenges the notion that the thalamus is more involved in lexical-semantic processing. The contribution of the thalamus in language is complex and fascinating, further studies are needed to determine fully the thalamic role in language.

4.4 Phonological short-term memory: supramarginal gyrus

The VBM analysis showed that the ability to repeat and write to dictation is dependent upon an intact supramarginal gyrus. Several studies have shown that the supramarginal gyrus plays an important role in verbal working memory, supporting the model of a *phonological loop* (or *articulatory loop*) (Paulesu et al., 1993) (Baddeley, 2003; Buchsbaum and D'Esposito, 2008; Henson et al., 2000; Ravizza et al., 2004). The phonological loop is one of Baddeley's proposed two passive slave systems within his model of working memory (Baddeley, 1968; Baddeley, 2003). According to this model, the phonological loop is responsible for temporarily storing verbal information, and is divided into two components; i.) a temporary *phonological*

store that holds memory traces over a short period of time, during which the memory traces decay, unless refreshed by the second component (Baddeley, 2003), ii.) the *subvocal rehearsal system* that refreshes and maintains information within the phonological store, as well as registering visual information onto the phonological store (provided that the visual information can be named) (Baddeley, 2003). Evidence in support of the phonological store is seen in the *phonological similarity effect*, where short-term memory is worse for similar sounding items, even when presented visually, while evidence for the rehearsal system is provided by the *word-length effect,* where the longer the items take to articulate, the worse the short-term memory (Baddeley, 2003; Buchsbaum and D'Esposito, 2008; Henson et al., 2000).

One of the first studies to look at the neural correlates of the two components of the phonological loop was a PET study reported by Paulesu and colleagues in 1993 (Paulesu et al., 1993). The study looked at the regional cerebral blood flow while healthy volunteers performed tasks designed to test different components of the phonological loop (i.e remembering strings of English letters for the phonological store, and rhyming judgement for the phonological rehearsal system). The results showed that activation in the left supramarginal gyrus correlated with the demands on the phonological store, while the subvocal rehearsal system was associated with Broca's area. The authors concluded that Brodmann's area 40 (the supramarginal gyrus) is the primary site for the phonological store. Since then, many studies have also looked at the neural correlates of the different components of the phonological loop and found similar results locating verbal representations in left posterior temporal areas, and short term storage in left supramarginal gyrus. (Henson et al., 2000).

Other have also suggested that the phonological store may not be a structurally localisable brain region, but instead is a state of functional brain activity (Buchsbaum and D'Esposito, 2008).

In summary, our current VBM analysis revealed that the supramarginal gyrus is involved in language production, and is crucial for the ability to repeat and write to dictation. However, whether this area is indeed the phonological store remains to be determined.

4.5 Limitations of the current study

Although statistical analysis was conducted on every voxel of the brain across all patients, the sensitivity of this analysis depends on the number of patients with lesions to each voxel. In our study, we had a good coverage of lesions along the perisylvian cortices in both the left and right hemispheres. With these regions, we were able to distinguish different lesions with different behavioural deficits. However, we did not have good coverage in the occipito-temporal areas that have been shown to be involved in many other aspects of language.

The second source of limitation is the use of multiple regression to tease apart the different effects of interest. Multiple regression is a good method for teasing apart different components since each regressor explains what cannot be explained or accounted for by all the other regressors, but it is not so effective at finding commonality between regressors. Also, in order to tease apart the effect of interest, other effects of no interest are factored out. This may result in the loss of valuable information.

As mentioned previously, our study did not look at the motor aspects of speech on their own, therefore our 'phonological retrieval systems' may also contain components of motor speech. Moreover, as mentioned previously, for the lexical phonological retrieval analysis, semantic-processing was not factored out. Thus, the regions associated with lexical phonology may also contain semantic-components. However, it may also be possible that lexical retrieval and

semantic retrieval are so closely related that they can not be separated. Thus further study is needed to confirm this point.

It is interesting to note that we identified one patient with a selective sublexical phonological retrieval deficit who had damage to the right posterior insula and thalamus. Since this patient did not contribute to the results of the VBM analysis, it is interesting to note that for this particular patient the deficit is caused by the predicted areas but in the contralateral hemisphere. Although the patient may have been right-hemisphere dominant, nevertheless this finding emphasises the variability across patient and reminds us of the danger and assumptions of over-interpreting individual lesion studies. Again further study is needed to understand the right hemisphere contribution to various linguistic tasks.

Conclusions

Language is one of the most complex abilities the brain performs. Our ability to communicate complex ideas and thoughts to each other is crucial in every aspect of life. When this complex ability fails due to injuries, the result is devastating. The aim of this study of the neuroscience of language is to understand the underlying mechanisms of language in order to help us to develop appropriate treatments. Since we do not fully understand the mechanisms of language in the brain, accurate prognosis cannot be given to the patients and their families. Better understanding of the neurology of language may also pave the way towards better treatments. The aim of our study was to investigate if we could indeed predict the precise behavioural deficits following lesions to particular regions of the brain. More research is needed, but our knowledge of language in the brain is progressing rapidly.

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